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THE AMERICAN
JOURNAL OF PHARMACY

JUNE, 1917

THE PHARMACY OF CALCIUM GLYCEROPHOSPHATE.

By James F. Couch, Washington, D. C.

The following communication contains an account of certain experiments designed to furnish knowledge of the behavior of calcium glycerophosphate in solution and the effect upon the salt of those substances which are commonly associated with it in pharmaceutical mixtures. In a consideration of this substance one must always remember that the commercial salt is a mixture of two isomeric compounds in varying proportions depending upon the details of manufacture; the isomerism being essentially that of substituted propyl and isopropyl groups. This fact in itself lends so much uncertainty to the chemical that no one would be justified in presenting the results of experiments in which the mixture had been used without a statement of the relative proportions of the isomers if the last Pharmacopœia did not recognize the mixture as the official substance. I have not been able to find a reliable method for the separation of the isomers and cannot, therefore, state the composition of the salt used in these determinations. Analysis, however, showed that it easily conformed to the tests of the Pharmacopœia.

In this investigation the first step was the compounding of the two preparations in the National Formulary which contain calcium glycerophosphate (if we are to have abbreviations why not "glycphos" instead of the longer official term?). It was found that the amount of calcium glycerophosphate directed was not completely soluble in either of the official menstrua, the consequence of which is that its proportion in the finished elixir will vary with the skill of the pharmacist, the temperature of the laboratory and the composition of the salt he employs. By directing the addition of purified talc to the compound elixir and immediate filtration the

National Formulary obscures the fact of the insolubility of the calcium glycerophosphate and the pharmacist may be led to believe—unless he be of a critical turn of mind—that each liter of his finished elixir contains 16 Gm. of calcium glycerophosphate.

The Compound Elixir of the Glycerophosphates, N. F. IV, was prepared with rigid adherence to the directions except that the purified talc was omitted and the mixture was not immediately filtered. A large proportion of the calcium salt was found out of solution, not having been dissolved and then precipitated on the addition of the alcohol which might have happened. It had never been dissolved and no other manipulation would cause its solution. This mixture was allowed to stand two days at room temperature with occasional shaking in order that there might be no doubt of the establishment of equilibrium. A considerable precipitate remained.

The mixture was now divided into four equal portions. The first portion was filtered, made up to volume through the filter, bottled and set aside for analysis. To the other three portions lactic, citric, and phosphoric acids were severally added in small amounts until the insoluble matter was dissolved. 4 Gm. of citric acid per liter dissolved the precipitate in one portion. This solution began to deposit calcium citrate within a week and the precipitation continued until the acid was exhausted. A third portion required 40 mils of U. S. P. phosphoric acid per liter to completely dissolve the precipitate and this solution quickly became cloudy as a heavy precipitate settled out. In the fourth portion the undissolved calcium salt was brought into solution by lactic acid in the proportion of 30 mils per liter and this solution, which was not filtered, shows only a barely perceptible cloudiness after standing three months. This mixture now contains 40 mils per liter of lactic acid which is sufficient to dissolve and retain in solution 16 Gm. per liter of commercial calcium glycerophosphate.

Lest the use of the term "commercial" in the above paragraph lead to misunderstanding let me add that the adjective was used to designate the mixture of isomers found in commerce which conforms to the requirements of the Pharmacopœia. All of the materials used in this investigation complied with the standards of the U. S. P. IX or N. F. IV, unless otherwise stated.

The first portion was analyzed for calcium glycerophosphate. 29.57 mils gave 0.00826 Gm. of calcium oxide corresponding to 11.72 Gm. calcium glycerophosphate per liter, or 73.36 per cent. of the formulated amount.

The discovery that the official elixir actually contains only 75 per cent. of the calcium glycerophosphate directed was disconcerting but not entirely unexpected, for after several years' experience with glycerophosphate mixtures I did not believe that the N. F. IV formula was so adjusted that it would dissolve 16 Gm. of the salt.

An experimental batch of elixir calcium and sodium gylcerophosphates N. F. IV was now made to determine the satisfactory character of this formula. The ingredients were manipulated according to the N. F. directions; the calcium salt completely dissolved in the diluted phosphoric acid: upon the addition of the sodium glycerophosphate solution a white precipitate appeared at first but redissolved when all the solution had been added. A faint cloudiness was produced when the glycerin was mixed in and this became pronounced when the aromatic elixir was added. The mixture was made up to volume with water which did not redissolve the precipitate; one half of the mixture was filtered, the other half was bottled without filtration.

The filtered portion precipitated within twelve hours: it was refiltered and allowed to stand. Another precipitate formed in four hours. Lactic acid was now added to this in the proportion of 15 mils per liter; the precipitate was redissolved and after standing three months the amount of precipitation was inappreciable. The unfiltered portion continued to precipitate until a large deposit covered the bottom of the container.

From these experiments it appears that neither of these formulas is wholly satisfactory. In order to compete with proprietary preparations now in commerce the compound elixir must contain approximately 8 grains and the dual elixir 4 grains of calcium salt per fluidounce.

One of the best known proprietary brands of the compound elixir was submitted to analysis. One fluidounce yielded 0.1186 Gm. calcium oxide, equivalent to 6.854 grains of calcium glycerophosphate. This preparation had apparently been filtered after precipitation: it was labelled 8 grains. Tests showed the presence of free phosphoric and lactic acids.

It was then decided that the solubility of calcium glycerophosphate should be determined under various conditions and, if possible, a combination was to be found which would retard the hydrolysis of the salt.

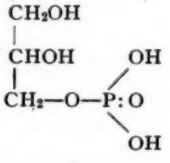
All work with the U. S. P. substance is complicated by the fact

that the solubilities of the isomers are quite different and where the relative proportion of the two is unknown one cannot adopt the usual method for determining the solubility of the salt—that of shaking the solvent with an excess of solute at definite temperature and analyzing the solution—for, as DuBois[1] has pointed out, such a solution will contain a larger proportion of the more soluble isomer than the original mixture. On the contrary, solvent must be added to a weighed portion of the salt until it dissolves in order that the solution may truly represent the original compound. To verify this the solubility of the salt was determined by each method. The first procedure in which an excess of salt was used gave a solubility in water of 1:31.59 at 25° C., while the second method yielded the result 1:56.95 at the same temperature. Most of the solubilities reported in the following experiments were determined by the latter method: the first method was used in some comparative experiments. All determinations were made at 25 degrees C.

Before entering upon a discussion of these determinations, however, we may profitably review the present knowledge of calcium glycerophosphate.

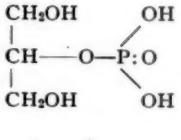
The U. S. P. IX states that its solubility in water at 25° is about 1:50; DuBois[1] says commercial calcium glycerophosphate should dissolve in 40 to 50 parts of water at 20 degrees. In this work the solubility was determined as 1:56.95 at 25°.

The commercial product is a mixture of α and β calcium glycerophosphates derived from isomeric α and β glycerophosphoric acids whose relationship is shown by the following structural formalas:



α

and



β

Salts of the diglycerophosphoric acids may also be present in the commercial salt as impurities but are excluded by the alcohol-soluble tests of the Pharmacopœia.

The solubilities of the isomeric calcium salts is given[1] as:

[1] "The Chemistry and Properties of Glycerophosphates," read before the pharmaceutical division of the American Chemical Society, September 10, 1913.

α (anhydrous)		1 : 22 at 20°.
α	"	1 : 108 at 100°.
α	"	1 : 22.4 at 16°. (Power and Tutin.[2])
β	"	1 : 60 at 20°.

Both isomers are insoluble in alcohol.

Acids increase the solubility of calcium glycerophosphate in water but those acids which form insoluble calcium salts gradually produce a precipitate in the solution, which is undesirable. In addition, any admixture with acid increases the rate of hydrolysis of the glycerophosphoric acid so that, even in the presence of acids which do not form insoluble calcium salts, a precipitate of secondary calcium phosphate may be produced unless the proportions of acid and salt are so adjusted that the soluble primary calcium phosphate is formed. Lactic acid appears to be eminently fitted for this purpose. Citric, phosphoric, and tartaric acids are objectionable because they lead to precipitation and other acids are excluded for therapeutic reasons or pharmaceutical inelegance.

Experimental.

1. *Influence of Alcohol upon the Solubility of Calcium Glycerophosphate in Water.*—For this purpose a solution made by saturating water with the salt at 25° was used. The solubility was 1 : 31.59.

A. To 35 mils of solution 1.5 mils of alcohol were added. A flocculent precipitate immediately appeared. The mixture was shaken and allowed to stand until precipitation was complete. The precipitate was filtered off, washed with a small quantity of 5 per cent. alcohol, dried at 110°, and weighed. Wt. ppt. 0.2308 Gm.

B. To 34.7 mils of mother liquor from experiment *A* 1.9 mils of alcohol were added. A precipitate was produced which was treated as in *A* except that it was washed with 10 per cent. alcohol. Wt. ppt. 0.2195 Gm.

C. To 33.8 mils of filtrate from experiment *B* 0.9 mils of alcohol were added. The precipitate produced was treated as in *A* and *B* except that it was washed with 12 per cent. alcohol. Wt. ppt. 0.1366 Gm.

Solution *A* contained about 5 per cent. alcohol by volume, *B* about 10 per cent. and *C* about 12 per cent. The solubility of calcium glycerophosphate in diluted alcohol at 25° is therefore:

[2] *Jour. Chem. Soc.*, 87, 240 (1905).

In 5 per cent. alcohol	1 : 41.6
In 10 per cent. alcohol	1 : 55.6
In 12 per cent. alcohol	1 : 66.6

assuming that the composition of the precipitate is the same as that of the original salt. The method here employed gives quantitative results only for the case where the solute is in excess as before stated. It does show, however, that small amounts of alcohol markedly repress the solubility of the salt.

2. *Influence of Acids upon the Solubility of Calcium Glycerophosphate in Dilute Alcohol.—A.* To 25 mils of the saturated solution used in the first series 0.33 mil of lactic acid was added. Alcohol was now added drop by drop and thoroughly mixed in until a permanent cloudiness was produced. The total volume was 31.9 mils. Allowing 3 per cent. for shrinkage the alcoholic content of the mixture was nearly 23 per cent. by volume and the solubility was about 1 : 40. Thus, 1 per cent. of lactic acid increases the solubility of the salt so that 23 per cent. alcohol equals the solvent power of 5 per cent. alcohol without such addition.

B. To the foregoing 0.9 mil of lactic acid was added which redissolved the precipitate. Alcohol was added to permanent cloudiness as before. The final volume was 101 mils and the alcoholic content nearly 72 per cent. The acid concentration was 1.22 per cent. and the solubility about 1 : 128. Without the acid calcium glycerophosphate would be scarcely soluble at all in 72 per cent. alcohol.

C. To 25 mils of the saturated solution 3.5 mils (12 per cent.) of alcohol were added. A precipitate occurred which was redissolved by 0.2 Gm. citric acid. Within twenty-four hours a crystalline precipitate of calcium citrate appeared.

D. To 25 mils of the saturated solution 3.5 mils of alcohol were added and 0.6 mil of U. S. P. phosphoric acid were used to redissolve the precipitate. This solution became cloudy in a short time, but did not deposit a precipitate.

E. To 25 mils of the saturated solution 3.5 mils of alcohol were added. 0.6 mil of lactic acid redissolved the precipitate. Solution has remained clear for three months.

3. *Influence of Glycerin upon the Solubility and Hydrolysis.—A.* To 75 mils of the saturated solution 25 mils of glycerin were added. In 8 days the solution became cloudy; in 7 days more a precipitate settled out.

B. On the same date 100 mils of a saturated solution of calcium glycerophosphate in water made by the second method was prepared and set beside the above solution, both being securely stoppered. This solution precipitated in three days and at the end of a month there was fully ten times as much precipitation in the aqueous as in the glycerin solution. These experiments show roughly that, while glycerin does not prevent the hydrolysis of the calcium glycerophosphate, it does retard it.

C. 1.75 Gm. calcium glycerophosphate were treated with 100 mils of a 25 per cent. solution of glycerin in water. The salt was not quite completely soluble. This quantity was just soluble in 100 mils of water.

D. To the foregoing solution 0.5 mil of lactic acid were added. The remainder of the calcium salt dissolved. The solution precipitated in the same fashion as in experiment *A* and to the same extent. This indicates that glycerin retards the hydrolysis in acid solutions also.

4. *Joint Influence of Alcohol and Glycerin on the Solubiliy of Calcium Glycerophosphate.—A.* An aqueous mixture containing 12.5 per cent. of alcohol, and 25 per cent. of glycerin was employed. 100 mils were added to 1.75 Gm. of the calcium salt. Very little dissolved. 3 mils of lactic acid were sufficient to effect the solution. This solution did not precipitate; in three months a small cloudiness only was visible.

5. Influence of sodium glycerophosphate solution upon the solubility of the calcium compound.

A. An aqueous solution of the U. S. P. solution of sodium glycerophosphate which contained 40 Gm. per liter (or the same strength that is used in the N. F. compound elixir) was employed to dissolve 1.75 Gm. of the calcium salt. Required 178.85 mils of solvent. Solubility, 1:102.2 at 25°. The calcium compound is, therefore, only half as soluble in this solvent as it is in water. In addition, this solution hydrolyzed rapidly.

6. Influence of alcohol, glycerin, and sodium glycerophosphate upon the solubility of calcium glycerophosphate in lactic acid solution.

A. 1.75 Gm. of the calcium salt were treated with a solvent composed of 12.5 per cent. alcohol by vol., 25 per cent. glycerin, 40 Gm. per liter of sodium glycerophosphate solution U. S. P. and 1 per cent. of lactic acid. Required 294 mils of solvent. Solubility, 1:168 at 25°.

The influence of sodium citrate upon the solubility was roughly determined. It was found that an admixture of 20 per cent. of this salt increased the solubility from 1 : 57 to 1 : 32 and that the solubility of calcium glycerophosphate in a 1 : 250 solution of sodium citrate was 1 : 41. Both of these solutions quickly precipitated calcium citrate.

Summary.

It has been shown that,

1. The solubility in water of calcium glycerophosphate is increased by acids and by sodium citrate.

2. The solubility in water is repressed by alcohol, glycerin, and sodium glycerophosphate solution.

3. Lactic, citric, and phosphoric acids increase the solubility in presence of alcohol or glycerin or both.

4. Acids hasten the hydrolysis of the salt-producing precipitates except that lactic acid tends to keep the hydrolytic products in solution.

5. Alcohol and glycerin repress the hydrolysis even in the presence of acids.

6. In the N. F. formula for the compound elixir the lactic acid should be increased to at least 40 mils, and in the formula for the calcium and sodium glycerophosphate elixir the phosphoric acid should be replaced by at least 20 mils of lactic acid.

Discussion.

The use of various acids in order to increase the solubility of calcium glycerophosphate so that an effective amount of it may be presented in the old-time teaspoonful dose, while highly necessary for pharmaceutical reasons, is, nevertheless, quite undesirable from chemical considerations. The addition of acid causes the formation of free glycerophosphoric acid, which undergoes autohydrolysis,[3] the free hydroxyls of the acid acting as the catalyst, so that, eventually, the mixture consists of a calcium salt, free added acid, glycerin, and phosphoric acid. There may then be little or no true glycerophosphates in the solution. Not only will this occur with the calcium salt but it will obtain with all glycerophosphates in acid solution. Self[4] suggested the addition of sulphuric acid in making acid glycerophosphates and DuBois[1] states that these compounds are

[3] Malengreu and Prigent, *Zeit. physiol. Chem.* (1911), 73, 68–84.

[4] *Pharm. Jour.*, May 16, 1908, p. 627.

less stable than the neutral salts. All the proposed formulas employ some acid: Dunning[5] used hypophosphorous acid, later changing to lactic; the Australian Pharmaceutical formulary,[6] Griffiths,[7] British Pharmacopœia,[8] all use phosphoric acid.

In addition to the objection which arises from the hydrolysis of the compound another, and more serious, danger bids us hesitate to add weak organic acids to such elixirs. The compound elixirs of the glycerophosphates all contain a quinine salt. It has been shown that weak organic acids cause an intramolecular rearrangement in quinine which results in the formation of quinotoxine,[9] a highly poisonous ketone to which fatal consequences have been attributed. No undesirable results from this cause have as yet been reported in the case of the glycerophosphate elixirs.

In view of these facts it would probably be best to eliminate liquid preparations of the glycerophosphates and to supply the small demand with tablets or powders. Whatever the therapeutic value of the glycerophosphates may be[10] their efficacy cannot be demonstrated to advantage by a liquid full of their hydrolytic products.

A discrepancy will be observed in the results for the solubility of the calcium glycerophosphate as observed in the compound elixir and in experiment 6*A*. The first shows a solubility of 1:85 while the latter gives 1:168. This is due to the fact that in the case of the elixir an excess of solute was present so that a larger proportion of the more soluble isomer entered solution than in experiment 6*A*.

AN INTERESTING PRESCRIPTION.[1]

By L. F. Kebler, Ph.C., M.D.

I desire to call attention to what appears to me a unique combination of drugs and some incidents connected therewith. A patient was suddenly taken seriously ill after taking some medicine put up

[5] *Proc. A. Ph. A.*, 54, 616 (1906).

[6] Druggists' Circular formula book, p. 6 (1915).

[7] "Non-Secret Formulas," p. 321 (1910).

[8] Quoted in Hiss and Eberts's "Pharmaceutical Preparations," p. 409 (1908).

[9] v. Miller and Rhode, *Ber.*, 28, 1056; Scoville, *Jour. A. Ph. A.*, May, 1916, p. 590.

[10] *Jour. A. Med. A.*, LXVII, No. 14, p. 1033 (September 30, 1916).

[1] Read at the Kansas City meeting of the American Chemical Society, 1917.

on order of a physician by a pharmacist. The medicine was suspected and immediately discontinued. The question naturally arose as to whether or not a mistake had been made in compounding the prescription, which was known to contain corrosive sublimate. The unused pills were turned over to me, a friend of the family, with a view of having the amount of mercuric chloride estimated, so that suitable treatment could be instituted if found necessary. A copy of the prescription, which follows, was procured:

℞ Hydrarg. Bichloride ..... Grs. ½.
Sulphur Præcip. ..... Drams 2.
Ol. Theobromæ ..... Q.S.
Pil. XXX.
Sig: One before meals t.i.d.
Dr. ————

It will be observed that this mixture calls for 1/60 of a grain of corrosive sublimate, 4 grains of sulphur, and an indefinite amount of cocoa butter to each pill. A number of points must be considered in making an examination of a mixture of this character. First, variability in the weight of the pills. Second, chemical reactions which may interfere with the estimation of the corrosive sublimate. Third, method of analysis. Fourth, uniform distribution of the mercuric chloride. These points will be taken up in the above order.

First, variability of weight of pills. Twenty of the pills were weighed with the following results:

	Grams.	Grains.		Grams.	Grains.
1.....	0.52	8.0	11.....	0.53	8.2
2.....	0.50	7.7	12.....	0.54	8.3
3.....	0.54	8.3	13.....	9.59	9.1
4.....	0.55	8.5	14.....	0.53	8.2
5.....	0.53	8.2	15.....	0.51	7.9
6.....	0.47	7.2	16.....	0.56	8.6
7.....	0.51	7.9	17.....	0.53	8.2
8.....	0.52	8.0	18.....	0.49	7.6
9.....	0.54	8.3	19.....	0.55	8.5
10.....	0.55	8.5	20.....	0.52	8.0

Weight.	Grams.	Grains.
Maximum	0.59	9.1
Minimum	0.47	7.2
Average	0.53	8.2

Percentage variation from the average: 2 slightly exceed a 10 per cent. variation from the average; 3 exceed a 5 per cent. variation from the average.

From a study of other subdivisions of medicines these variations, considering the character of the article, are reasonable.

Second, chemical reactions. There appeared to be no reaction at the time the material was received, nor at the end of two years. In discussing this matter with the prescribing physician he stated in substance that this mixture enabled him to give very large doses, as large as 2 grains of the mercuric chloride, without any untoward effects. He considered this a very important observation in that it may be possible by this mixture to inhibit undesirable intestinal fermentation. It was suggested that possibly the mercury may be converted into an insoluble sulphide, thus rendering it inert, but no information on this point has been found.

Third, method of analysis. It can readily be seen that the large amounts of sulphur and cocoa butter would tend to make the determination of the mercuric compound rather difficult. Neither incineration nor sublimation was possible. A little experimentation showed that petroleum ether dissolved the sulphur and cocoa butter and practically none of the mercuric chloride. The method used for estimating the mercury compound was as follows:

A number of pills, accurately weighed, were introduced into a beaker, a sufficient amount of petroleum benzin was added to completely disintegrate the pills and dissolve the greater portion thereof; the mixture was then transferred to a separatory funnel, the beaker rinsed with several successive portions of the benzin and transferred to the above separatory funnel. The benzin mixture was then treated with several successive portions of water, acidulated with hydrochloric acid, the successive aqueous portions transferred to a beaker through a funnel, in the throat of which a pledget of cotton was lodged. After the benzin solution was completely extracted with the acidulated watery solution and the latter transferred to the beaker, the mercury was precipitated with gaseous hydrogen sulphide. The mercuric sulphide obtained was transferred to a weighed Gooch crucible provided with a suitably prepared filter, the precipitate washed with water, then with alcohol, and finally with ether to dissolve any free sulphur. The crucible and contents were then dried to constant weight at 110° C. in a hot air oven and the weight determined. From the data available the amount of mercuric chloride was calculated. The amount found was somewhat less than called for by the prescription. The pharmacist apparently endeavored to lean on the side of safety in filling an order calling for so potent a poison to be taken internally.

Fourth, uniformity of distribution. It is of course impracticable to analyze each pill separately, but an examination of several successive portions showed that the distribution was fairly uniform.

In conclusion it should be stated that if this mixture were given to a chemist for analysis without any knowledge on his part as to the presence of the mercuric chloride he would in all probability overlook it.

BREEDING FOR ATROPINE[1]

GREAT VARIATION IN ALKALOIDAL CONTENT OF BELLADONNA PLANTS PROMISES RESULTS TO SELECTION—EXTERNAL CHARACTERS OF PLANT SEEM TO GIVE A CLUE TO ITS CHEMICAL CONTENT.

By L. Wayne Arny, Director H. K. Mulford Co., Experimental Drug Gardens, Glenolden, Pa.

The high prices paid for crude drugs, brought about by the abnormal economic conditions of the last few years, have stimulated a wide and popular interest in the cultivation of the plants yielding these products. Unfortunately for the crude drug industry, a great part of this interest has been aroused merely from a view toward financial investment and the real issues at hand have been generally overlooked.

There is no question but that America must grow a large part of her drug supply in the future since the drug importations are yearly becoming less dependable. The adulterations which are being made by collectors of crude drugs render the purchase of these plants upon the open markets extremely unsatisfactory and if the American manufacturer of pharmaceuticals is to produce articles of high grade, he must either grow his own vegetable drugs or obtain them from someone who he knows is growing them honestly.

Certain economic facts, however, must be considered. Competition with European peasant labor greatly reduces the chances of financial profit from American production, and unless some step can be taken to produce drugs superior to those of European origin, no hope can be found for such an industry in America upon a purely financial basis. It is probable, however, that such improvement can be brought about, and the competition will be changed from quantity

[1] Reprinted from *Jour. Heredity*, April, 1917, Vol. III.

against quantity to quality against quantity. Stating the case in a more simple way it may be said that financial success in the cultivation of drug plants depends upon the possibility of increasing the alkaloid content of these plants by plant breeding methods.

The object of this paper is to point out to breeders who are interested in this field of work the opportunity which these plants offer for selective methods of improvement. The resulting improvement from research work in this direction not only will afford the satisfaction which is coincident with accomplishment, but will provide raw materials of uniform and high quality to the exacting professions of medicine and pharmacy. This surely then is a worthy field for experimental effort. It at once becomes evident that the work of increasing alkaloids in a plant differs from that of increasing size, changing color or form. The investigator is dealing with unseen characters.

Little Hybridization Done

Hybridizing drug plants has been attempted by several workers and under varying conditions but in general little result has been gotten from this method. There may be exceptions to this statement, such as cinchona;[2] but especially with plants of the temperate zone, the great majority of crossing experiments have resulted only in a chaotic jumble of characters without meaning. This is to be expected when we keep in mind the class of plants with which we are dealing.

The most serious effort then must be through selective methods, but here again certain difficulties at once arise. Since the characters with which we are working are unseen, the number of individuals that can be placed under observation is therefore limited, and in turn the chances of success are proportionately reduced.

In establishing a system of selection of belladonna[3] (*Atropa Belladonna*) at the Mulford Drug Gardens, the effort was made to overcome this difficulty by establishing a correlation between some apparent physical character and alkaloidal content. If such a corre-

[2] The South American cinchona tree, from the bark of which quinine is secured, has been improved by breeders in Java, who have selected the best of many natural hybrids, and propagated them asexually. This is usually referred to as the only drug plant which has been improved through hybridizing; but so far as I am aware, there is no record of really scientific breeding having been done with it.

[3] For an outline of some similar work with belladonna and other plants, see "Breeding Medicinal Plants," by F. A. Miller. *American Breeders' Magazine*, IV, pp. 193–201.

lation could be demonstrated, the advantage of observing thousands of individuals rather than hundreds would be at hand.

The breeding plot contained 500 individuals which were chosen from a lot of several thousand seedlings. The seed from which these plants were grown had been imported from Germany and no previous history of them was known. They were sown in the greenhouse in January and potted off in the usual manner. Those used for the breeding plot were chosen only because of uniform size and apparent vigor. Some of the features of the plant were recorded on a card at the time of setting out. These included size in its first and second weeks, and when adult; the blooming date, color, size of leaf and of root, and any other facts which seemed likely to be of interest. The plot contained five rows with 100 plants in each row numbered chronologically and recorded on individual cards. These plants were examined once each week for the first three weeks and then as often as the data on the cards required. The soil on which the plants grew was a heavy clay loam with a clay subsoil and had received no treatment except a heavy application of stable manure during the winter.

The leaves were gathered at the usual time—just as the flowers are opening—and enough leaves were allowed to remain to mature the fruit pods. The leaves were then air dried on drying racks in bundles corresponding to the plant from which they were taken, after which they were assayed for alkaloidal content. The error incident to this process was minimized by running the assays in duplicate. Of the 400 samples, 15 were discarded because too small, or because they were spoiled in assaying. The alkaloidal content of the remaining samples, expressed in percentages, was as follows:

Alkaloidal Content,	Number of Samples.
.0–.09	4
.1–.19	8
.2–.29	26
.3–.39	83
.4–.49	94
.5–.59	65
.6–.69	42
.7–.79	26
.8–.89	25
.9–.99	6
1.0–	6
	385

Mean = .507; σ = .194.

The standard of the United States Pharmacopeia is 0.4 atropine in belladonna, and the average sample found in the markets varies from this minimum to about 0.6. It is evident, then, that nearly 70 per cent. of the plants were above the standard in chemical content, and that six of them yielded 1 per cent. or more of atropine—a remarkably high percentage. They were as follows:

1.020
1.000
1.100
1.230
1.030
1.039
Avg. 1.07

Interest naturally centered on these plants, and a study of the records showed that every one of them was small at the time of harvest, while practically all the plants which yielded .01 or less were large and vigorous in growth. Furthermore, the six high plants all had light stems, while the plants yielding .1 or less had dark stems. These characters were the only ones found which seemed to give a clue to the chemical constitution of the plants, but they were marked enough to warrant especial attention during the coming season, when a selected second generation will be grown.

In conclusion, it must be remembered that this work covers only one season and hence must be regarded as merely preliminary. It is highly encouraging to us, however, in indicating the extreme variation of atropine content in the belladonna plant and giving hope that valuable commercial results can be secured by selection.

SOME CONSTITUENTS OF JAMBUL.[1]

By Merrill C. Hart and Frederick W. Heyl.

The Jambul Tree (*Syzygium Jambolana*), well known to the natives of the East Indies and Malay regions from China to New South Wales, for its edible fruit, is a large tree belonging to the *Myrtaceae*, sometimes attaining the height of ninety feet. A careful gleaning of the medical literature finds that three parts, the seed,

[1] Reprinted from the Journal of the American Chemical Society, Vol. XXXVIII, No. 12, December, 1916.

pericarp and bark, have been employed in the treatment of *diabetes mellitus* with questionable results, but is perhaps impressed by some beneficent results reported. Two parts of the plant, the bark and the pericarp, have been recognized in the pharmacopeia of the Netherlands.[2]

The berry-like, sour fruit is about as large as the olive, and apparently forms a readily procurable commodity in the European market, whereas the term Jambul as used in this country refers to the flinty, hard seed contained in the pericarp. There is also some difference in opinion as to the part of the plant which should be employed in the manufacture of the fluid extract.

The early chemical studies showed the presence, in the bark, of tannin,[3] in the seed, of gallic acid.[4] The seed yields a trace of ethereal oil, 0.37 per cent. fat, and 0.3 per cent. resin, and pharmaceutical shrewdness, rather than chemical investigation, or conformance with a rational system of nomenclature, has given the name "antimellin" to an alleged glucosidic constituent.[5] This finding of Börsch could not be substantiated by Power and Callan.[6] The statement of Pottiez[7] concerning the presence of quercitol and cinnamic acid could not be confirmed by these chemists. Stephenson[8] found that the diastatic hydrolysis of starch was appreciably reduced by the presence of the extract of the fresh kernels.

Several preparations of German origin are marketed, *e. g.*, Djoeat, Bauers, Glykosolvol and Pavykol, which probably contain, in part, extracts from the bark or pericarps, and Djoeatin (Börsch) which is alleged to contain the above-mentioned "antimellin." The presence of tannin has recommended its use among the natives as an astringent, but on the whole, as stated in the Dispensatory, "it has failed to establish itself as a practical medicament."

The recent work of Power and Callan on Jambul seed leaves the question as to the pharmaceutical value of the pericarp. It was our plan to make a comparative study of the seed and pericarp, and we decided to investigate independently the seed, while awaiting a promised supply of pericarp, which unfortunately will not be available at present and we therefore report our work on the seed.

[2] *Ph. Nederl.*, IV.
[3] Johanson, Dissert., Dorpat, 1891.
[4] Elborne, *Pharm. J.*, 3, 932 (1888).
[5] Börsch, *Pharm. Ztg.*, 44, 574 (1899).
[6] *Pharm. J.*, 34, 414 (1912); 91, 245 (1913).
[7] *Ann. Pharm. Louvain*, 5, 373, 490 (1899).
[8] *Pharm. J.*, p. 211 (1892).

Our sample of Jambul seed, which was badly worm eaten, was received from Bombay. It was picked over and 91 pounds were rejected from a 200-pound shipment. The material contained 8.0 per cent. moisture and 2.9 per cent. ash. Ligroin extracted 1.2 per cent., ether, 1.3 per cent., and alcohol 16.1 per cent. The residue insoluble in alcohol had the following composition: crude fiber, 2.3 per cent.; pentosans, 2.1 per cent.; protein, 6.3 per cent.; starch, 41.4 per cent.; dextrin, 2.1 per cent. The alcohol extract showed the presence of 0.3 per cent. sucrose and 3.3 per cent. reducing sugars. Tannin amounted to 6.0 per cent.

The products present in the alcoholic percolate, and soluble in water, besides the sugars and tannin, are ellagic and gallic acids.

The study of the resin gave, in general, the same results as those reported by Power and Callan, *i. e.*, from the ligroin extract, oleic, linoleic, palmitic and stearic acids; from the ethyl acetate and alcoholic extracts, chiefly ellagic acid. We are, however, able to describe more fully the presence in the ligroin extract of myricyl alcohol, of a hydrocarbon very probably hentriacontane, and of a phytosterol, $C_{27}H_{46}O$, melting at 135–135.5° that formed an acetate, melting at 119–120°. The ether extract as well as the chloroform extract yielded in addition a phytosterolin, $C_{33}H_{56}O_6$, which we have described in detail.

We endeavored to repeat Stephenson's work which would indicate the presence of something in Jambul that would retard diastatic hydrolysis. In using the iodine method of Sherman, Kendall and Clark,[9] it was found to be impossible to read the end points of a diastatic hydrolysis because the presence of gallic acid in the extract decolorized the iodine solution. In the same way the reducing action of a Jambul extract is sufficiently great to render inaccurate their excellent gravimetric method employed for finding the activity of pancreatin.

EXPERIMENTAL.

(*A*) PROXIMATE ANALYSIS.—A sample of the air-dried seed after grinding and sieving was quantitatively extracted with various solvents, with the following results:

Extract	Percent.
Ligroin (35–55°)	1.2
Volatile ether extract	0.2
Ether	1.3
Alcoholic	16.1

[9] *American Chemical Journal*, 32, 1073 (1910).

The proximate analyses were conducted in accordance with the usual methods, and gave the result tabulated below:

	Percent.		Percent
Moisture	8.0	Protein	6.3
Starch (diastase)	41.4, 40.3	Ash	2.9
Crude fiber	2.3	Dextrin	2.1
Pentosans	2.1	Tannin[10]	6.0

The quantitative examination of the alcohol-soluble carbohydrates resulted as follows:

100 g. of Jambul seeds were extracted with boiling 95 per cent. alcohol. The alcoholic extract was concentrated to a syrup, precipitated with a slight excess of lead subacetate and made to a volume of 200 Cc. The direct and invert readings at 22° in 2 dcm. tube are —2.6V, and 3.2V, respectively.. The invert reading at 86° in a 2 dcm. tube was 0.35V. Hence sucrose = 0.23 per cent., fructose = 2.3 per cent., and glucose = 2.1 per cent., respectively. Gravimetric determinations by the Walker-Munson process gave sucrose 0.33 per cent. and reducing sugar 3.3 per cent.

(*B*) Examination of Alcoholic Extract.—For this purpose 45.4 kg. were exhausted by percolation with wood alcohol at room temperatures. Power and Callan extracted the seed with hot ethyl alcohol. The percolate (397 l.) was concentrated under diminished pressure to a volume of 12.5 liters. This concentrated extract on standing deposited 230 g. of yellowish material which was quite insoluble in the usual organic solvents. It could be redissolved in dilute alkali and then reprecipitated by the addition of acetic acid. After being digested with ether, and with ethyl acetate, this material was crystallized from pyridine. Brown needles were obtained that gave the characteristic tests for ellagic acid.

The filtered alcohol extract was poured into 25 l. of distilled water and vigorously agitated. After long standing the resin was removed by filtration. The aqueous alcohol filtrate was concentrated under reduced pressure in order to remove the alcohol. When this solution was diluted with distilled water, further precipitation took place even after diluting to a volume of 80 liters. The solution was allowed to stand overnight and the precipitate (372 g.) was filtered off. This material was of the nature of a phlobaphene. The filtrate was concentrated to a volume of 9.77 l. It now deposited 84 g. of ellagic acid. This deposit was digested with ether and

[10] Both the Hide powder method, and the Proctor-Lowenthal method gave the same results.

with ethyl acetate and crystallized three times from pyridine. The crystals were washed successively with water, ethyl acetate and ether, dried at 150° and analyzed.

Calc. for $C_{14}H_6O_8$: C, 55.6; H, 2.0. Found: C, 55.6; H, 2.1.

The aqueous solution containing 5276 g. of water-soluble plant extractive was divided and a quantity containing 3750 g. was extracted repeatedly with large volumes of ether, which extracted 524 g. of a greenish white solid, which proved to be gallic acid. This amounts to 1.63 per cent. of the drug. A portion of this crude gallic acid was digested with fresh ether, which removed the color. The residue crystallized from water in colorless needles, decomposing at about 240°. It was dried at 115° and identified as gallic acid:

Calc. for $C_7H_6O_5$: C, 49.4; H, 3.5. Found: C, 49.4; H, 3.4.

The dark green ethereal filtrate from the purified gallic acid was exhaustively examined, and a small quantity of sulfur melting at 114–115° was identified as a constituent.

The aqueous solution which had been completely extracted with ether, was now extracted with chloroform, which extracted only 3 g. of material. This was redissolved in chloroform and fractionally extracted with the usual alkaline solvents which yielded nothing definite. The neutral solution upon evaporation yielded a minute quantity of crystalline material melting at 115–121°. This gave the color tests of the phytosterol group.

The aqueous solution which had been completely extracted with ether and chloroform was now extracted repeatedly with hot amyl alcohol. During this extraction there ensued a gradual precipitation of ellagic acid. The material extracted with amyl alcohol weighed 742 g., equivalent to 2.2 per cent. of the drug. This extract contains a considerable quantity of ellagic acid. The amyl alcoholic extract could be prepared as a greyish white powder, by precipitation with petrolic ether. From dilute alcohol and from pyridine solutions, ellagic acid separated. A part (58 g.) of the amyl alcoholic extract was redissolved in this solvent and the solution was extracted with the usual alkaline solvents, but nothing crystalline was separated by this procedure. Another part (127 g.) was hydrolized by boiling for several hours in the presence of 5 per cent. sulfuric acid, but no crystalline hydrolytic products

were found. Eighty-four grams were hydrolized by boiling for one minute with 10 per cent. potassium hydroxide solution. The mixture was cooled and poured into an excess of dilute sulfuric acid, and then steam distilled. From the contents of the flask a quantity of gallic acid, melting at 240–242°, was isolated.

A quantity (171 g.) was boiled with a large volume of water and then vigorously steam distilled. Ellagic acid separated. The solution was concentrated and further quantities of ellagic acid separated. At length, after evaporation to dryness, the residue was boiled with ethyl acetate and some insoluble material (ellagic acid) was removed by filtration. It was impossible to obtain crystals from this solution. The ethyl acetate solution was evaporated to dryness, and again taken up in dry ethyl acetate, in which it was freely soluble, but nothing definite could be obtained from it. The amyl alcoholic extract is not glucosidic.

The aqueous liquid which had been extracted with ether, chloroform, and with amyl alcohol, was freed from the latter immiscible solvent by a vigorous steam distillation. The distribution of nitrogen in this solution was as follows: Total soluble nitrogen, 0.0649 per cent.; ammonia nitrogen, 0.0079 per cent.; lead subacetate precipitable nitrogen, 0.0197 per cent.

In order to test for acid amides, one fifth of the solution was precipitated with mercuric acetate solution, but the results were negative.

The remainder of the solution was precipitated with basic lead acetate, filtered, and the precipitate was found to consist essentially of lead tannate.

The filtrate from the lead tannate was freed from lead with hydrogen sulfide and sharply concentrated. Although this syrup yields a precipitate with phosphotungstic acid, no nitrogenous bases were isolated from this fraction. The only product found was sugar, a crystalline deposit of a *d*-phenylglucosazone melting at 207–208° being readily prepared. Pentose sugars were absent.

THE EXAMINATION OF THE RESIN.—The resin which precipitated when the alcoholic extract was poured into water weighed about 699 g., equivalent to 1.5 per cent. of the drug. It was dissolved in wood alcohol, poured upon purified sawdust, transferred to a continuous extractor, and extracted with the following results:

Ligroin (40–60°)	433 g.
Ether	20
Chloroform	13
Ethyl acetate	79
Alcohol	109
Total	654 g.

THE LIGROIN EXTRACT.—Three hundred grams were dissolved in ether and shaken with solutions of potassium hydroxide (5 per cent. and 10 per cent.). The alkaline extractions were acidified and extracted with ether. This ethereal solution was successfully extracted with a solution of ammonium carbonate (10 per cent.) but these extracts yielded nothing but a small quantity of smeary material precipitable with acid.

The ethereal solution was now extracted with solutions of potassium carbonate, and the fatty acids occurring free in the plant were removed. The alkaline extract containing the potassium salts of these fatty acids was acidified and extracted with ether. The ethereal solution of fatty acids was dried over anhydrous sodium sulfate. The ether was removed and a residue of about 92 g. obtained. This was distilled under diminished pressure. The boiling point was 215–250° at 20 mm., and the iodine number of the distilled acids which solidified in the receiving tube was found to be 88.7. A very considerable quantity of this material could not be distilled and it remained as a tar in the flask. These fatty acids were studied in connection with those obtained upon the subsequent hydrolysis of the glycerides.

The ether solution which had been extracted with ammonium carbonate and potassium carbonate was now extracted with a solution of potassium hydroxide. The alkaline extract was acidified and a quantity of tarry material (15 g.) precipitated. This was dissolved in alcohol and subjected to acid and alkaline hydrolysis, but nothing crystalline could be separated in either case.

The ether solution which had been extracted with solutions of ammonium carbonate, potassium carbonate and potassium hydroxide contained 17 g. of neutral material belonging to the unsaponifiable material. It boiled at 120–250° at 15 Mm., and yielded oily distillates exactly corresponding to those described among the unsaponifiable products of the fat.

The original ethereal solution of the fat which had been extracted with solutions of potassium hydroxide was evaporated to

dryness and the residue was saponified by boiling with 250 Cc. of 10 per cent. alcoholic potash for about five hours. The alcohol was removed and water added to completely precipitate the unsaponifiable material, which was extracted with ether.

EXAMINATION OF THE UNSAPONIFIABLE MATTER.—The dried solution was evaporated to dryness and the residue was an orange-colored oil amounting to 47 g. It was dissolved in absolute alcohol and upon standing 0.15 g. of material separated. The melting point was indefinite (62–76°) and suggested, as stated by Power and Callan, a mixture of hydrocarbon and a higher alcohol. By means of the phthalic acid fusion, and subsequent extraction with sodium carbonate, a small quantity of a hydrocarbon melting at 61° was isolated. Three crystallizations from ethyl acetate raised this melting point to 63°. It separated in colorless leaflets and was perhaps impure hentriacontane.

Calc. for $C_{31}H_{64}$: C, 85.3; H. 14.7. Found: C, 85.1; H, 14.1.

A small quantity of a sodium salt of an acid phthalic ester was isolated and boiled with alcoholic potash. A product separated which had the melting point of myricyl alcohol, 82–84°. It crystallized from alcohol in leaflets, which softened at 82° and melted at 85°.

Calc. for $C_{30}H_{62}O$: C, 82.2; H, 14.1. Found: C, 81.7; H, 13.5.

The alcoholic solution from which the hydrocarbon and myricyl alcohol had separated yielded no further crystallizations even from concentrated solutions after the addition of small quantities of water. This residue was distilled under diminished pressure.

Fraction I (b. p. 120–160° at 100 Mm.). This was a colorless, limpid oil with a fragrant odor. The weight was 11 g.

Fraction I (b. p. 120–160° at 10 Mm.). This was a colorless, oil, less mobile than the first fraction, and of about the same weight. A systematic fractional distillation of I and II effected no separations.

Fraction III (b. p. 200–250° at 10 Mm.). This was a thick viscid oil which partially solidified. It weighed about 5 g.

The fractions collected above 250° at 10 Mm. solidified in the receiver. The fraction boiling at 280–340° at 10 Mm. was crystallized from ethyl acetate. The material melted at about 132°, but

softened somewhat lower. It was necessary to separate a small quantity of low-melting material (70–75°) by a fractional crystallization and phytosterol then separated in glistening plates, melting sharply at 135–135.5°.

Calc. for $C_{27}H_{46}O \cdot H_2O$: H_2O, 4.5. Found: 5.6 per cent.

Calc. for $C_{27}H_{46}O$: C, 83.9; H, 11.9. Found: C, 83.8; H, 11.6.

0.1163 g. of the anhydrous phytosterol made up to 20 Cc. with chloroform showed a rotation of —0.489 in a 2 dcm. tube, whence $[\alpha]_D^{25} = -42.04°$.

It yielded an acetyl derivative that separated from acetic anhydride in thin plates which melted at 119–120°.

EXAMINATION OF THE FATTY ACIDS.—The alkaline solution from which the unsaponifiable matter had been extracted with ether was acidified and the liberated fatty acids were extracted with ether. The ether solution was dried over anhydrous sodium sulfate, concentrated to a small volume and then largely diluted with ligroin which precipitated some tarry material. This was removed by filtration, and the solvent was distilled from the fatty acids. These boiled chiefly at 230–260° at 15–20 Mm. A small fraction distilled at 260–280° at 20 Mm. The weight of distilled acids was 30.1 g., and the iodine number was 98.3.

These acids were mixed with those which had been extracted with potassium carbonate solution. A portion weighing 22.5 g. was converted into the lead salts, which were treated with ether. The liquid acids obtained from the lead salts soluble in ether weighed 12.9 g. (57.3 per cent.). These boiled chiefly at 235–245° at 32–34 Mm.

Calc. for $C_{18}H_{34}O_2$: C, 76.6; H, 12.1; iodine no., 90.1; for $C_{18}H_{32}O_2$: C, 77.1; H, 11.4; iodine no., 181.4. Found: C, 76.6, 76.7; H, 11.3, 11.55; iodine no., 131.7.

The liquid acids therefore consist of a mixture of oleic and linoleic acids.

The lead salts of the fatty acids, insoluble in ether, were decomposed with hydrochloric acid and the solid fatty acids separated in the usual manner. When dissolved in absolute alcohol with the object of separating any of the more insoluble acids by crystallization, it was found that the acids were very readily soluble and no satis-

factory crystallization could be obtained even from very concentrated solutions. The alcoholic solution was fractionally precipitated with an alcoholic solution of barium acetate. This yielded Fractions I and II. Fraction III was precipitated by the addition of water.

1. Melting at 51–53°. C, 75.8; H, 12.4; N. v., 204.3.

III. This fraction was an oil and gave entirely anomalous analytical data. Iodine no., 35.2, 34.7; neutralization value, 34.9; and saponification value, 140.2.

The solid acids are therefore a mixture of palmitic and stearic acids.

Calc. for $C_{16}H_{32}O_2$: C, 75.0; H, 12.5; N. v., 219.1. $C_{18}H_{36}O_2$: C, 76.1; H, 12.7; N. v., 197.5.

THE ETHER EXTRACT OF THE RESIN, which amounted to 20 g., contained a quantity (2 g.) of an insoluble white solid. This was filtered off. When this substance was dissolved in chloroform, in the presence of a few drops of acetic anhydride, and sulfuric acid was added, a play of colors resulted showing at first transient pink, then blue, and finally a beautiful green. It was crystallized several times from dilute pyridine, and then melted at 275–285°. It was a phytosterolin. After being dried to constant weight at 120° it was analyzed.

Calc. for $C_{33}H_{56}O_6$: C, 72.3; H, 10.2. Found: C, 72.3; H, 10.2.

A portion of this was converted into an acetate, which crystallized from dilute alcohol in colorless, glistening leaflets melting at 167–168°.

0.5036 g. of the anhydrous phytosterolin acetate, when made up to 20 Cc. with chloroform, showed a rotation of —1.21° in a 2 dcm. tube, whence $[\alpha]_D^{23} = -24...$

One gram of this phytosterolin was hydrolyzed according to the method outlined by Power and Salway.[11] It was dissolved in 60 Cc. of hot amyl alcohol and 20 Cc. of an aqueous 15 per cent. solution of hydrochloric acid added, together with sufficient ethyl alcohol to form a homogeneous liquid. After heating for three hours in a reflux apparatus, steam was passed through the mixture to re-

[11] *J. Chem. Soc.*, 103, 399 (1913).

move the amyl alcohol, and the contents of the flask then filtered. A solid substance was thus collected, which after several crystallizations from ethyl acetate, alcohol, and dilute alcohol, separated in glistening leaflets melting at 134–135°. The mother liquors from this crystallization contained a relatively large quantity of an oily resinous material which had evidently been formed from the phytosterolin by too prolonged hydrolysis. The crystals gave the phytosterol color reaction.

0.0983 g. made up to 20 Cc. with chloroform had a rotation of 0.38° in a 2 dcm. tube, whence $[\alpha]_D^{25} = -38.8$.

Calc. for $C_{27}H_{46}O$: C, 83.9; H, 11.9. Found: C, 83.3; H, 11.3.

The acid aqueous liquid, from which the phytosterol had been separated by filtration, was exactly neutralized with sodium carbonate, evaporated to dryness, the residue digested with absolute alcohol, and the mixture filtered. On evaporating the alcoholic filtrate a small amount of syrupy residue was obtained, which reduced Fehling's solution, and yielded an osazone melting and decomposing at 212°. It was thus evident that the sugar was glucose.

Thus this phytosterolin is shown to be phytosterol-*d*-glucoside.

The ether extract from which the phytosterolin had been separated was fractionally extracted with varying strengths of alkali. The potassium hydroxide extracts removed practically all the dissolved matter as a green oil which after some time became semi-solid. This could not be crystallized and was unchanged when boiled for several hours in the presence of an alcoholic solution of 5 per cent. sulfuric acid solution.

The Chloroform Extract of the Resin weighed 13 g. Part of this extract was quite insoluble in ethyl acetate and alcohol with which it was digested. This part was crystallized twice from dilute pyridine and melted at 280–295°. This gave the usual color test for a phytosterolin. After crystallization it weighed 3 g. Altogether the phytosterolin isolated from the ether and chloroform extracts amounted to 5 g. or 0.011 per cent. of the air-dried drug.

The filtrate from the above phytosterolin was evaporated to dryness, taken up in chloroform, and then fractionally extracted with varying strengths of alkali. Nothing of a crystalline nature was obtained by this procedure.

The Ethyl Acetate Extract of the Resin was a mixture of ellagic acid and tannin-like substances. Upon distilling off a por-

tion of the ethyl acetate about half of it separated as crude ellagic acid, which when crystallized once from alcohol yielded 13 g. of pure acid that did not melt at 350°. The mother liquor from this separation was a smear, that colored ferric chloride solution black, and precipitated a gelatin solution.

The part soluble in ethyl acetate was thoroughly examined but nothing was isolated.

THE ALCOHOLIC EXTRACT OF THE RESIN yielded 15 g. further of ellagic acid. The total ellagic acid separated amounts to 1.2 per cent. of the plant. Neither an acid hydrolysis nor a potash fusion gave any interesting decomposition products. Neither the ethyl acetate fraction nor the alcoholic extract was glucosidic.

KALAMAZOO, MICH.

METHODS OF STUDYING COAL[1]

HOW A NEW METHOD OF REFINED TECHNIQUE HAS REVEALED PLANT RECORDS TO THE INVESTIGATION, ESPECIALLY WITH REFERENCE TO THE ORIGIN OF COAL.

BY E. C. JEFFREY.

Coal, since it is a mineral, has in the past been investigated with the aid of the admirable technical processes, which have been devised by the mineralogist and petrologist in the study of minerals and rocks. Fossil plants, also, have naturally been regarded as minerals, since in the condition ordinarily studied structurally they are petrified: that is, infiltrated or, in some instances, actually replaced by mineral substances. In addition to the relatively scanty petrified remains of fossil plants, which have previously been the most important document for the student of extinct vegetations, there are huge quantities of plants of former epochs, preserved for us by a more or less complete process of carbonization. This carbonization is so marked in some instances, that it is obvious that the plant remains have been charred previous to fossilization. The present writer has turned his attention to the utilization of these carbonized remains, in connection with the tracing of the all too incomplete geological records of plants. By the perfecting of processes

[1] Reprinted from *Science Conspectus*, Vol. 6, No. 3, 1916.

of softening and bleaching these carbonized remains, it has been found possible to add very largely to our knowledge of the organization of ancient plants, particularly of the Mesozoic Age, concerning which our information has been most meager. Methods developed first for the investigation of isolated members and parts of plants, by modification have proved serviceable in the study of that structurally almost unknown mineral coal. Our ignorance of the organization of coal is not due at all to the neglect of mineralogists, but rather to the unsuitability of the approved methods of their science in the case of a substance at once so opaque and so friable. The advantages of the methods recorded here may be judged from the fact that they permit the cutting of large quantities of sections, which average one tenth of the thickness of the few and laboriously secured preparations resulting from the grinding processes of the mineralogist. Moreover it is possible to render the sections even more favorable for study for bleaching, which is inapplicable to ground sections. It should be added that the successful manipulation of the processes described in the subsequent paragraphs involves a considerable experience in the use of the microtome, the slicing mechanism of the biologist.

The more recent and less modified coals are treated for sectioning with comparative ease. Alcohol alone is frequently sufficient to bring about the necessary degree of softening for successful slicing. Such coals are of relatively light hue, and sections need not be so thin as is essential in the case of the older and more highly carbonized coals. In general, however, somewhat vigorous softening agents must be used in the investigation of combustible minerals, since pressure and temperature have often brought about a considerable degree of modification even in coals of tertiary and secondary origin. Caustic soda or potash dissolved in alcohol of about 70 per cent. strength in the proportion one part in ten is a very useful preliminary reagent but has been found for various reasons, less valuable in use than phenol. This substance has unfortunately advanced immeasurably in cost on account of its employment as a basis for the manufacture of high explosives in the present European war. The phenol or carbolic acid is melted and the selected coal samples (which must ordinarily not be more than a centimeter in length and breadth by half a centimeter in thickness vertically) are subjected to its action. The material is to be kept hot in a water bath for a number of days, usually as long as a week. The

carbolic acid is then washed out with repeated changes of warm water. Heat and subsequent treatment with water after neutralization by means of an acid are likewise necessary in the case of material treated with alkaline alcohol, as described above. The advantages of the use of phenol in softening coal are that less swelling and cracking results than in the case of alkaline alcohol, and the material is in better condition for subsequent manipulations.

The removal of mineral substances from the coal is the next stage and for this purpose hydrofluoric acid is most generally employed. The fragments of coal remain in strongest commercial hydrofluoric acid for some days or even a week or more. In the case of coals neither much carbonized nor possessing a very high proportion of ash, the processes indicated suffice. In most coals, particularly those of the Paleozoic period, after treatment with hydrofluoric acid, the combustibles must be washed for a day or two in running water and then returned to the phenol for a renewed sojourn in the heat. This second softening in many cases is sufficient, but where a higher degree of carbonization is present, a second treatment with hydrofluoric acid is needed. In still more resistant coals the processes must be further repeated and the acid is reinforced in its action by adding crystals of chlorate of potash or soda, which brings into play the activity of nascent chlorine. With anthracites and other coals of an extreme degree of carbonization, nitric acid may be added with advantage to the hydrofluoric acid and chlorate of potash, but in moderation so that maceration may not result. The treatment with hydrofluoric acid and accompanying reagents, where these are necessary in the case of more refractory coals, is carried on in wax bottles or in glass bottles coated both externally and internally, with hard paraffine or beeswax. A fume-cupboard with heavily painted windows is safe and convenient for this work, particularly if it is built over a soapstone sink.

After the coal is softened and bleached (as is the case where chlorates and *aqua regia* are used), it is carefully washed in running water until quite free from the reagents. In the case of highly bituminous coals, particularly cannels and the like, the pieces may be returned to melted phenol for some days. With most coals, especially those of later geological ages, it is necessary to wrap the specimens with bands of cotton fabric, held in place by stout linen thread. This precaution prevents the coal from going to pieces in the phenol. After the last treatment with carbolic acid, the combustible is washed

repeatedly with warm water and then transferred to strong alcohol and finally to absolute alcohol, to remove all the water. Two or three changes of absolute alcohol are necessary. After the water is entirely removed the specimens are exhausted of all air under an air pump of high vacuum. In order to secure slices of the softened coal, it must be held together by means of nitrocelluloses. The best and least explosive of these is Schering's Celloidin, which is for the moment practically unobtainable on account of the war. It may be replaced with some degree of success by Anthony's photographic cotton. This is a less pure nitrocellulose and gives results which are less satisfactory. The dehydrated and air-free coal is transferred into a 2 per cent. solution of nitrocellulose in absolute alcohol and ordinary ether (of good quality). Absolute methyl alcohol gives better results than ethyl alcohol and is sold by the Bausch & Lomb Optical Company under the commercial name of Synthol. The material is secured in a strong bottle by means of a good cork wired in and remains for a day in a bath kept at the temperature of 70° Centigrade. It is allowed to cool and then transferred to a 4 per cent. solution of nitrocellulose in the medium indicated above. A second twenty-four hours in the heat brings it to a 6 per cent. solution. After the latter treatment it is enclosed in an air-tight chamber made from large diameter steam pipe. The corks are removed from the bottles preliminarily and by means of a valve in the cap of the chamber and an automobile pump, pressure is raised to two hundred or more pounds. The coal remains under these conditions over night and has then become thoroughly infiltrated with the solution of nitrocellulose. The next step is to transfer it to a thick solution of nitrocellulose. In this it is placed again in the warm bath and after a time still further thickening is brought about by the addition of dry fragments of nitrocellulose. After several days of repeated thickening the specimens are now ready for the final process. This consists of transferring them from the thick nitrocellulose to chloroform. Chloroform has the valuable property of at once hardening the nitrocellulose and further softening the coal. After a stay of some hours in chloroform, which must not be used sparingly, the piece of coal are transferred to a mixture of equal parts of alcohol and glycerine, where they may remain indefinitely, until needed for sectioning.

The fragments of coal treated in the manner described above are clamped in a heavy sliding microtome (the Jung-Thoma modified to the author's design answers very well for this purpose). A very

sharp and heavy knife is employed for sectioning and its edge must be kept moistened with ordinary strong alcohol. The sections are turned back on the knife, as they are sliced, by means of a large camel's hair brush, wet with alcohol. Successful sections must usually be five micromillimeters or thinner. If the processes have been successfully carried out, abundant and consecutive slices can easily be secured, showing every feature of organization of the coal.

After the sections are cut they are dehydrated by means of absolute alcohol, to which a quantity of chloroform has been added to obviate the softening of the nitrocellulose in the coal. From the absolute alcohol and chloroform they are transferred to benzole or some other clearing medium and are then mounted in hard Canada balsam, dissolved in benzole or whatever clearing agent has been used on the sections. Where too high a degree of clearing is undesirable, as for example in the case of oil shales, chloroform may with advantage replace benzole or xylol. After the covers are put on, the preparations are allowed to dry for a day in a horizontal position and they are gradually warmed up with lead weights on the covers to promote flattening. When the balsam has become so thickened by the heat as to set in the cold, the slides are cleaned up. Where it is necessary to make photomicrograms of them, they are still further flattened by means of a clip clothes pin acting on a disk of cork (over the cover) in the heat of a warm bath. For photographic reproduction, the best lenses (Zeiss apochromatics) are desirable and these should be used with a yellow screen and chromatic plates. Screens of other colors, although theoretically more desirable than yellow, have not been found practically to give as good results, probably on account of the difference between the visual and chemical focus even in the best microscopic lenses. The largest possible amount of light should be used, an end to be attained both by having a powerful electric arc as a source of illumination and the diaphragm of the sub-stage condensor opened to the widest possible degree, consistent with sharp focusing of the object. Naturally only the very best lenses will give good results under these conditions. The details of photomicrography are so familiar to all scientific workers in the field here described, that further details will only add unduly to the length of this article.

In conclusion are added, at the editor's request, some statements in regard to the bearing of the results obtained by the technical manipulations described upon the problem of the mode of formation of coal. It is to be noted that the mass of expert opinion at the

present time regards coal as of the nature of modified peat and as having originated in most cases on wet land as the result of the rooting, flourishing and falling of successive generations of plants on the prostrate remains of their ancestors. This condition is realized in the cold, temperate regions of our earth. In the tropics, however, in spite of a luxuriance of vegetation, with which that of the greatest coal age (Carboniferous) has been frequently compared, there are no accumulations of vegetable matter on the soil. In warm climates the hoarding of plant remains occurs only in the bottoms of lakes and tranquil estuaries, since the high temperature makes the destruction of dead vegetable matter on land particularly rapid. Even in this country, which, as a whole, is neither particularly hot nor especially cold, we have the authority of the United States Bureau of Mines (Peat Investigations) for the statement that by far the greater accumulations of vegetable matter occur under open water, which by its relatively constant level, safeguards the hoardings in its depths from the ravages of destroying fungi, since these are unable to flourish subaqueously.

The investigation of coals from all parts of the world and from every geological age, by the methods described in the earlier paragraphs, has made it clear that, in general, coal is of the nature of impude cannel. It is universally conceded that cannel coals, oil shales and similar combustibles, which constitute a small proportion of coals mined, were laid down in open water. We can best picture their mode of deposition by reference to a lake of to-day. Generally in the month of June the forest trees shed their fertilizing dust (pollen) in the air, to be borne by the winds to the waiting seeds. Most of the blossom dust is spilled, however, on the bosoms of lakes, lying in sheltered hollows, where the air currents losing their driving force drop their load of pollen, which falls on the waters as so-called "sulphur showers." After floating for a while in circling windrows, the pollen sinks with other coarser vegetable matter into the depths of the lake or estuary. Where the pollen or spores were relatively abundant in the depths of the coal lakes of the past the result was a deposit which later became a cannel or oil shale. In more troubled and shallower waters a greater amount of the vegetative parts of plants accumulated with the spores and pollen, to constitute the raw material of a "fat" bituminous coal. Where the vegetative parts predominated a "lean" type of coal is the final result. Often in addition to spores we find in coal wood with structure preserved, most inappropriately designated "Mother of Coal."

This constituent, which is the record of ancient forest fires, frequently retains its organization so perfectly that it is possible to diagnose the type of tree from which it was derived. If the wood was only partially charred by the action of heat, its persistence as such in coal is correspondingly incomplete. Sections of coal ordinarily reveal two sorts of material showing recognizable structure: namely, "Mother of Coal" (relatively rare) and spores or pollen of the higher or vascular plants (more or less abundant). In addition to these structurally preserved constituents, combustible minerals are largely formed of a brown matrix resulting from the modification in the course of ages of the uncharred woody and other gross vegetable remains. With the fundamental brown of highly modified wood, the spores contrast by their golden yellow hue and "Mother of Coal" by its intense black (shading into brown in those portions incompletely charred). The mass of the coal has been subjected to enormous compression during the ages elapsed since its deposition in the bottom of the waters. As a consequence even its structural constituents are greatly flattened in the plane of the horizontal bedding or laminaion.

The study of ultimate organization now rendered possible by improved technique appears to finally set at rest the controversy which has lasted for nearly a century and a half, in regard to the origin of combustible minerals. The generally accepted view of the way in which coal has been formed is that it is essentially, dynamically and chemically transformed peat. This conception which took its origin with von Beroldingen in the eighteenth century, has had its main defenders in Germany and as a result of the Teutonic scientific hegemony in modern times has been widely adopted in all parts of the world. In contrast to this hypothesis is the more logical view, cherished mainly in France, that coal is the consequence of organic sedimentation in open water. This opinion has been ably defended by Renault, Grand'Eury and many others, and there appears now no doubt that it is the correct one, since all the data derived from the microscopic study of coal, which must apparently ever be most cogent, are entirely in its favor. We must accordingly regard the hoardings of past plant life, preserved for us in the form of the various coals and their products, petroleum and natural gas, as having accumulated not in peat bogs but at the bottom of tranquil lakes, not *in situ,* but as the result of water transports.

Botanical Department, Harvard University,
February, 1916.

CORRESPONDENCE.

Representation of Pharmacy on the Council for National Defence.

Dear Brother Pharmacists:

Notwithstanding that this communication is printed, it is important to every pharmacist and to the country-at-large, and the only reason for sending you the matter in this way is on account of the haste that is necessary in order to do effective work.

The letter herewith is taken from one by President F. J. Wulling, of the American Pharmaceutical Association, addressed to the Secretary of War. It explains itself and no further comment is necessary in that respect. The short letter is one that was dictated to a Senator and will serve as a guide for writing to your Senators and Congressmen, and the other one will serve for the substance of a letter to the Secretary of War. As he has already been apprised of the pharmacists' desire, you can be very brief in your communication, but let your letter inform him of the object you have in addressing him.

The writer is certain that your Association will favor the effort which the American Pharmaceutical Association is making, and therefore either the secretary or president alone or the executive committee should be in position to at once address the Secretary of War and Senators and Congressmen. Quick work is the important thing and we hope that you will give this matter your very prompt attention. Let them know the strength of your organization, and if advisable, the number of druggists in your state.

May we say in this connection that the American Pharmaceutical Association is alive to the interests of American pharmacy and is only handicapped because of insufficient members. Let us therefore urge that at your forthcoming meeting you make the strongest effort possible to persuade as many to join the Association as possible. We believe that it is a duty of all pharmacists to belong to the American Pharmaceutical Association, and then they receive the benefits that this Association offers in its *Year Book* and *Journal*. The American Pharmaceutical Association has done great work in behalf of pharmacy. Its *Proceedings*, the *Year Book*, the *Journal*, the Pharmacopœia, the National Formulary, the work of the Drug Trade Conference speak only in part of this.

At this time the object of the communication is centered to enlist your support in securing due recognition for pharmacists in the government service and particularly apprise the government officials that pharmacists can be of efficient and valuable service. Your prompt coöperation will therefore be appreciated.

Thanking you and with fraternal greetings,

THE JOURNAL OF THE A. PH. A.

E. G. EBERLE,

Editor.

It appears that pharmacy has no adequate representation in the Army and Navy and that no representation has been accorded it on the Council for National Defense. Medicine is strongly represented. Medicine is not pharmacy, nor does it include pharmacy, as evidenced by the existence of the separate pharmaceutical profession. National defense without adequate pharmaceutical representation and recognition can never be as effective as it can be with pharmaceutical participation under proper standard of recognition. Medical men are not pharmacists and, as far as I know, do not claim to be. They cannot any more give expert pharmaceutical service than pharmacists can give medical or surgical service. In the failure to recognize and employ the expert pharmaceutical services available, the country falls short in that degree, as I see it. It is fallacious to claim that pharmaceutical service in war or peace is negligible or of so low a grade that it shall be a hand-maiden to any other division of the service.

The Council for National Defense has appointed a committee of which the Secretary of War is chairman, to effect, among other things, a practical standardization of pharmaceutical supplies. Who is as competent as a highly trained expert pharmacist to direct this standardization and other purely pharmaceutical activities? Unless this kind of work is under the direction or responsible participation of such a pharmacist, the country is deprived of the best kind of service in this field and yet it is entitled to the very best that the country affords. This kind of expert service is freely at hand and available and, as president of the American Pharmaceutical Association, I respectfully request and urge that it be employed. I feel that if I did not make this request and make it with the fullest strength of whatever influence my office carries, I would not be doing my duty to my country, not to speak of my duty to my calling.

It should be considered that in a crisis such as the United States finds itself in at the present time it is unwise for the country to risk the possible displeasure of so large a part of the representative citizens as pharmacists constitute. There are probably in excess of 500,000 persons engaged in pharmaceutical activities. These are represented in a large measure by a number of strong national and state associations—among them the American Pharmaceutical Association, the National Association of Retail Druggists, the American Conference of Pharmaceutical Faculties, the National Wholesale Druggists' Association, the American Drug Manufacturers' Association, American Association of Pharmaceutical Chemists, National Drug Clerks' Association, the Drug Trade Conference, *the several state associations* and others. The good will in the fullest measure of all these is essential. I do not maintain that these interests would withhold their good will if not given deserved recognition and the opportunity to serve in their fullest capacity, but I do maintain that proper recognition would greatly stimulate and augment their help and loyal support.

I desire to further direct attention to the unfortunate fact that the United States has not a pharmaceutical corps for the control and direction of medical and pharmaceutical supplies service such as all other great countries, except Great Britain and Russia, have. In each of these large countries a corps of highly trained pharmacists with commissioned rank has the medical and pharmaceutical supplies service in its hands. The head of the service in Germany is of the rank of Colonel; in Japan, of the rank of Lieutenant-Colonel; in Italy and France, of the rank of Major-General. These officers are experienced pharmaceutical chemists of high attainments and qualifications, capable of directing their respective service. Our own country contains many such men who are at least as capable, if not more so, for this kind of service as a surgeon could possibly be. That American pharmacy is not represented in the country's service in the form of a pharmaceutical corps composed of men equal in rank to those in the medical service is undoubtedly due to the fact that American pharmacy has not exerted that pressure for this merited recognition and opportunity to serve under its own responsibility and standard that it is capable of. Much dissatisfaction in this respect on the part of representative pharmacists in all divisions of the calling has been reported to me recently. It is my opinion that the country cannot afford to continue to ignore American pharmacy as it has done in the past.

In my humble opinion, if the post of Chief Medical Purveyor is not already in existence, it ought to be created and put in charge of an expert pharmaceutical chemist of administrative ability. Such a one should be clothed with ample authority and should be of the rank not lower than that of Colonel. The importance of the medical and pharmaceutical supplies service can hardly be exaggerated. The Hospital Steward of the present should not be confounded with the highly trained pharmaceutical chemist of administrative capacity I have in mind. Our late war with Spain demonstrated the utter inadequacy and futility of methods then in use for the purchase, manufacture and distribution of pharmaceutical and medical supplies.

In writing thus I know that I am representing American pharmacy at large, but of course I have only the authority vested in the office I hold to speak for the American Pharmaceutical Association.

I mean no disrespect to anyone. What I have said and urged grows out of my loyalty to the country and the cause it is championing and to our calling.

My urgent suggestion is that every national and state association appoint forthwith with the greatest dispatch strong and capable representatives to constitute a Council or Commission to bring about deserved and adequate pharmaceutical representation in the Army and Navy and on the Council for National Defense. This isn't the time for futile and undirected talk and discussion but for determined, insistent and fruitful action. *This is the psychological moment.*

A Letter to Congressmen and Senators.

(This letter was written by a pharmacist and may be used as a guide.)

As you know, American pharmacy feels that it has not proper representation and recognition in the government service. It has just come to my attention that the Council for National Defense has appointed a committee to effect, among other things, a practical standardization of pharmaceutical and medical supplies. The Secretary of War is chairman of that committee. It appears that no pharmacist is on the committee. For that reason I have written the Secretary of War in the matter. American pharmacists cannot understand why the government treats pharmacy so shabbily and medicine so generously. Here is an opportunity for someone to right a wrong and to earn the everlasting appreciation and thanks of pharmacy.

I do not want to take too much of your time, but in case you

would care to have me do so I will be very glad to take the matter up further with you and go into details.

PHARMACEUTICAL CORPS IN THE U. S. ARMY.

PHILADELPHIA, May 11, 1917.

Hon. Nelson D. Baker,
Secretary of War,
Washington, D. C.

Dear Mr. Secretary:

The Board of Directors of the Philadelphia Drug Exchange earnestly urges the establishment of a Pharmaceutical Corps in the U. S. Army analogous to the Medical Corps, the Dental Corps and the Veterinary Corps, for the following reasons:

1. The present system of enlisting pharmacists in the Army, *not* as pharmacists, but as privates, is hopelessly antiquated. France, Germany, Japan and other foreign countries have a Pharmaceutical Corps in their armies in charge of a pharmaceutical expert.

2. The present system is unjust to pharmacy and pharmacists. Pharmacy is a profession and the pharmacist of to-day has had years of collegiate training and practical experience in scientific work. To enlist professional men as privates is not only unjust to the men, but is unjust to the Army, because it denies to the Army the possibilities of service which such men could render.

3. The present system is faulty. The status of pharmacists in the Army is very unsatisfactory. Officially, they are not pharmacists, but non-commissioned officers with responsible duties and no possibility of advancement in the Service as pharmacists. They can excel as privates and be promoted as privates, but they cannot excel as pharmacists and be promoted as pharmacists; and this injures the service.

4. The present service is detrimental to the efficiency of the Army itself, because it fails to recognize the importance of proper and sufficient pharmaceutical service and denies to the sick and wounded the best pharmaceutical service that the Nation can give.

5. The present system is unfair to the medical corps, because it denies that body the assistance and support that a properly trained pharmaceutical corps could give. The pharmaceutical service could be made most valuable to the medical profession, not only in the hospitals, but also in the field.

Pharmacists have been trained, not only in the science and art of pharmacy, but also have had elementary instruction in some of the medical sciences, and with but little extra training could be made useful "medical assistants" in the field in the matter of surgical anesthesia, surgical dressing, etc., thus supplementing and helping the medical service.

We are informed by the Dean of a medical school in Philadelphia that 14,000 physicians will be required for an army of a million, that there are less than 7,000 physicians with ages of less than 31, and that, of these, probably one-half are physically unfit for service.

If this is correct, then only one fourth of the necessary medical material is available. In view of such a possibility, it seems to us that pharmacists could be made, with extra training, most valuable "medical assistants" in the field, while in the hospitals they could be given charge of the medical supplies of the hospitals, and render pharmaceutical and chemical service in the compounding and dispensing of drugs and in the chemical and bacteriological examination of excrements, foods, water, milk, etc.

Again urging the establishment of a Pharmaceutical Corps in the Army as most essential for proper pharmaceutical service, we remain

Yours respectfully,

(Sgd.) JOHN FERGUSSON,
President.

(Sgd.) J. W. ENGLAND,
Secretary.

QUARTERLY REVIEW ON THE ADVANCES IN PHARMACY.

BY JOHN K. THUM, PH.G., GERMAN HOSPITAL, PHILADELPHIA, PA.

POTASH.—According to Commerce Reports, a company making Portland cement at Durham, Ont., is now turning out as a by-product from the feldspar used, from twelve to sixteen tons of potash daily. Chlorides and caustic products are produced, the former being said to be an almost pure product. It is said that even the dust and

gases of the plant are trapped, in which there is said to be five per cent. of potash, which is used for fertilizer. It is also said to be quite possible for every cement plant in Canada, within the next five years, to produce potash in large quantities as a by-product. As is well known, there are immense deposits of feldspar in Canada, which are said to contain at least ten per cent. of potash, of which 86 per cent. in a pure form is collected. And it is also stated, and this is most important, the cost of manufacture is less than the freight charge per ton on that heretofore coming from Germany (*Jour. A. M. A.*, March 24, 1917, p. 917).

ANTIDRUG BILL.—The bill known as the Whitney antinarcotic act was endorsed by representatives of the New York State and New York County Medical societies and of the Medical Economic League at a hearing, March 22. This bill provides for a free supply of drugs for addicts and for the registration of addicts. Some of those present offered objection to the triplicate order blank system of checking narcotic drug distribution. However, this part of the proposed bill is under consideration with a view to formulating some plan which will not work undue hardship on practicing druggists (*Jour. A. M. A.*, March 31, 1917, p. 987).

PATENT LEGISLATION.—At the January meeting of the Philadelphia Branch of the American Pharmaceutical Association two interesting papers on the fore-mentioned subject were read. The subject is a timely one and one that affects the great mass of people very closely; this point should be played upon very insistently so as to get Congress to act. Never has the time been so favorable for legislation of this character. In the first paper Mr. J. W. England mentions that the crux of the situation in connection with the patenting of chemicals in this country is the system of permitting *product-protection;* he then goes on in a convincing manner and points out how this impedes the progress and development of American chemical industry. Dr. F. E. Stewart in his paper gives a most comprehensive discussion of the Paige Bill. This paper is enlightening in many ways and should be read by all chemists and pharmacists (*Jour. A. Ph. A.*, Feb., 1917, pp. 120 and 122).

PHARMACOLOGY OF THE ACONITES.—Of the vast number of the *Aconitum,* and there are at least 150, only two or three have been examined pharmacologically. Notwithstanding the fact that all those examined show the same characteristic results on the nervous system, secretions, circulation, and respiration, yet they may be

divided into two classes. One of those examined acts principally on the circulation, and the other on the respiration. Those containing aconitine belong to the first class, and those which contain pseudo-aconitine belong in the other class. *Aconitum Napellus* is the most efficient of the aconitine class. To the other class belong *Aconitum heterophylloides* and *Aconitum magarum;* these can be conveniently referred to as the pseudo-aconitine group. (*Jour. Pharmacology,* Chem. Abstr., 1917, II, 70, T. R. Fraser).

Elimination of Strychnine by the Kidneys.—According to the researches of the investigators named below this alkaloid makes its appearance in small quantities in the urine within a few minutes of administration, and the amount excreted is very much increased by diuresis. Injected intravenously large doses of the alkaloid do not increase the amount of excretion. It was found that in the case of dogs, renal excretion is not sufficient to save life, no matter how active it may be. It is therefore logical to assume that diuresis helps very little to the successful treatment of strychnine poisoning. It was also discovered that the amount of strychnine eliminated by the kidneys by dogs agrees generally with the amount eliminated in the same way by man (R. A. Hatcher and M. J. Smith, *Jour. Pharmacology,* Chem. Abstr., 1917, II, 69).

Banana Stalks as a Source of Potash.—The continued high prices for potash and the constant demand for it, for use as a fertilizer, has caused attention to be directed to many vegetable sources of this alkali. These sources have hitherto been disregarded as a means of potash production, but since the Stassfurt mines are no longer accessible, the world has been sad put for this very necessary adjunct to agriculture, and industry in general. Among the many sources mentioned banana stalks seem to show much promise. A recent investigation shows that banana stalks contain as much potash as, or nearly as much as, dried kelp as a filler for commercial fertilizers. The stalks, when charred and lixiviated, will produce 27 pounds from one ton of stalks, containing at least 90 per cent. of K_2CO_3. Further investigation may reveal more possibilities (*J. Ind. Eng. Chem.,* 153, 1917).

Destruction of Fly Larvæ in Manure.—No doubt the logical way to get rid of the ubiquitous fly is to destroy him before he reaches his full development. Therefore the results of the U. S. Department of Agriculture's experiments as to the best way in which to destroy the larvæ, should be of interest. After three

seasons the department feels safe in saying that one of the most efficient substances for this purpose is borax. Two pounds of this chemical to 28 gallons of water, which should be sufficient for 24 bushels of manure, is the most effective and cheapest of all the many substances tried. However, it must be used with a great deal of care, for if the manure is to be used for fertilizing purposes an excessive amount of the borax will be very prone to have an injurious effect on growing plants. They also found that 8 ounces of green hellebore to 10 gallons of water for the treatment of 8 bushels of manure, is also effective. Of course the cost is somewhat higher. Calcium cyanamide was also found to be of value for this purpose, a half pound of it to each bushel being the proper proportions. While the cost of this is higher, the manurial value is considerably increased; it is as well to add to it then at least half a pound of superphosphate as this chemical prevents the loss of ammonia by the action of the cyanamide, and in turn this adds to the increase of the phosphorus content. Good results were also obtained with solutions of aniline and emulsions of nitrobenzene with fish oil soap, this being found to be without harm to the fertilizing value of the manure. They advise against the use of such potent substances as potassium cyanide, Paris green, arsenic sheep-dip, and pyridine, it being claimed that these substances are too dangerous (F. C. Cook and R. H. Hutchinson in U. S. Depart. Agric. Bullet., 408).

Yellow Soft Paraffin as an Intestinal Lubricant.—There is considerable objection being manifested against the use of the liquid paraffin for internal consumption because of leakage; despite this disagreeable feature the popularity of this kind of treatment for habitual constipation is growing more and more every day. It is proposed by the writer that the soft paraffin be used to overcome this tendency of leakage; it is claimed that it is more thoroughly mixed with the intestinal contents and for this reason is more thoroughly lubricating. The author feels that it is greatly to be preferred to any form of oily enema (H. Gifford, *Jour. A. M. A.*, 304, 1917).

Chlorazene.—This article, made in this country, has antiseptic qualities and the claim is also made that it is an active germicide. Its action is somewhat similar to the hypochlorites, but is less irritating. Chemically it is known as sodium para-toluene sulphochloramine. It appears as a white crystalline powder, and has a chlorine odor. Chlorazene is not intended for internal administration; ex-

ternally it is used in solutions varying from 0.5 to 4 per cent. in strength. It can be dried at or exposed to a temperature of 100° to 102° C. without decomposition taking place.

Toxic Effect of Emetine Hydrochloride.—Two American Army physicians in a study of 140 cases of endometric dysentery treated with this drug, show that it is well to watch patients very closely who are being treated with emetine. They state that the danger is somewhat similar to that of salvarsan in the treatment of syphilis. Two of the patients died from conditions in no way connected with the disease for which they were being treated, while five others showed unusual symptoms, which, in the absence of any other known causes, were naturally attributed to the emetine. In the two fatal cases there was the inability to swallow water after food had reached the gullet; the heart was rapid and uncontrolled; there was a marked tendency for the head to fall forward, and there was a lobar-pneumonia. In the five other cases the symptoms were similar, all of which disappeared when the treatment ceased (Military Surgeon, 40, 58, 1917, Johnson & Murphy).

Infusion of Broom Tops as a Larvicide.—A cold infusion made by steeping fresh crushed tops in water for from ten to twelve days, in a quantity sufficient to give to the liquor a greenish color, was found to be a quite formidable agent of destruction for caterpillars. It was found to be of great benefit for watering cabbage as it readily destroyed the larvæ of the cabbage butterfly and other numerous larvæ which feed on cruciferous plants. In France it has been found to be particularly valuable for removing *Cochylis* larvæ from vines and various caterpillars from apple trees. The infusion is applied by simply spraying or watering over the plants (*Rev. Sci., L'Union pharm.*, through *The Phar. Jour. & Pharmacist, 2*, 1917, 17, p. 139).

New Method for Determining Ozone.—It is said that the following method for determining the presence of ozone used for surgical and therapeutic purposes is simple, accurate, and sensitive. This determination depends on the extreme avidity of ferrous ammonium sulphate for ozone, a reagent which is quite stable towards ordinary atmospheric oxygen under the conditions of the test. The reagent consists of 3.92 grams of ferrous ammonium sulphate dissolved in water and 20 mils of pure H_2SO_4, sp. gr. 1.815, made up to one liter. This is quite permanent under ordinary conditions. Against this, a solution of potassium permanganate, 0.316 gram is

standardized. To determine the amount of ozone in the air of a room, a liter flask filled with water is emptied therein. The air replaces the liquid. Five mils of the standard ferrous ammonium sulphate solution is then run into the flask and gently agitated. It is then at once titrated with the standard permanganate solution, five mils of which will equal to 0.4 Mn. of oxygen. The statement is made that as little as 0.00002 gram of ozone may be detected in this way, since one drop of the permanganate is sufficient to impart a pink tint to five mils of the ferrous solution. That this latter is perfectly stable towards atmospheric oxygen is shown by the fact that no oxidation can be detected when 20 liters of air free from ozone is slowly bubbled through it. It is interesting to know that when large volumes of ozone have to be dealt with, fully as good results can be gotten by employing standard solutions of ten times the strength mentioned above. When this was done, though, it was noticed that the more concentrated standard solution of ferrous ammonium sulphate, which contained 39.2 grams of the salt to the liter, was not so permanent as the more dilute solution (*Comptes rend.*, 1917, 164, 430, through *Pharm. Journal and Pharm.*, April 7, 1917, p. 295).

Influence of Carbohydrates on the Accuracy of the Van Slyke Method in the Hydrolysis of Casein.—The presence of carbohydrates during the hydrolysis of casein by the method mentioned above causes a complete redistribution of the amino-acids, which varies according to the nature of the carbohydrate. It is very marked in the hexone bases, and a considerable loss of amino-nitrogen also takes place when the protein is hydrolyzed in the presence of xylan. Direct hydrolysis is, therefore, without reliance when used for the estimation of amino-acids in feeding stuffs; the great variation in the nature and the amount of the carbohydrates in feed stuffs makes it impossible to establish factors of correction for the results (*J. Biol. Chem.*, 1916, 241–249, through *Analyst*, March, 1917, p. 90).

Hydrotropic Phenomena.—C. Neuberg cites a number of instances of this useful phenomenon, which is the property of aqueous solutions of certain salts dissolving certain other substances which by themselves are insoluble in plain water. This property or phenomenon has been termed hydrotropism and has been made use of pharmaceutically, the caffein sodiosalicylate of the National Formulary being an instance. Among the substances having this property

are benzoic, salicylic, benzo-sulphonic acid, and various hydro-aromatic acids. Solution of these substances will dissolve or increase the solubility of carbohydrates, alcohols, aldehydes, proteins, alkaloids, fats, and lipoids, and quite a number of other substances. This ought to open up an interesting field of experimentation among pharmacists for making solutions for hitherto insoluble drugs. As an example we might mention mercury salicylate. This drug is very popular among physicians, who are, because of its insoluble nature, compelled to give it in an oily suspension (*Biochem. Zeit., J. Chem. Soc.*, 110, 2, 555).

Relative Toxicity of Stovaine and Novocaine.—According to Hatcher and Smith, who have given considerable attention to the study of these two drugs, stovaine is slightly more toxic than novocaine when administered in like manner. Recovery from toxic doses of stovaine is not so prompt as from corresponding doses of novocaine. They found no evidence to show that stovaine exerts any direct action on the blood-vessels after the intravenous injection of it in cats and practically none of the drug was excreted unchanged in the urine of these animals. Stovaine, they say, causes death by bringing about immediate and simultaneous paralysis of the heart and respiration, the action of each being independent of that on the other (*Jour. of Pharmacology*, 1917, 9, 4).

Estimation of Fluorine in Soluble Fluorides.—A neutral solution of the fluoride is heated to boiling, and powdered calcium sulphate is added; after standing for one hour, with frequent stirring, the precipitate, consisting of calcium sulphate and calcium fluoride, is washed several times by decantation and collected on a filter. The latter consists of a disc of filter paper fitted into the bottom of a perforated platinum crucible. The precipitate is now washed (the wash water used should be saturated previously with calcium sulphate and calcium fluoride), then rinsed into an ordinary platinum crucible, and the water evaporated; the disc of filter paper is, meanwhile, ignited on the crucible lid and the ash introduced into the crucible. The dry contents of the crucible are then heated at 300° C. for one hour, or until constant in weight, then sulphated, again heated at 300° C., and weighed. The increase in weight after sulphating is due to the replacement of two atoms of fluorine by the sulphuric acid radicle, and a simple calculation gives the quantity of fluorine present. The error of the method is about 0.1 per cent. (*Amer. Jour. Sci.*, 1916, 42, 464–468, through *The Anaylst*, March, 1917, p. 93).

IMPORTANCE OF THE VARRENTRAPP REACTION IN FATS AND OILS.—Notwithstanding the fact that hydrogenation in the presence of a catalyst is the usual way of converting unsaturated fatty acids into saturated ones, it seems possible that some of the older processes could be carried out on a commercial scale with the means now available. This applies especially to the Varrentrapp reaction, in which oleic acid is converted into palmitic acid by fusion with an excess of an alkali hydroxid. The reaction is not confined to oleic acid; all unsaturated acids may be converted into saturated acids of lower carbon content. It is said that the process as outlined is satisfactory: For whale oil; 2,500 kilos of the whale oil fatty acids are placed in an autoclave of 5,000 liters capacity, 800 kilos of sodium hydroxid dissolved in an equal quantity of water are added, and the mixture is heated at 260° C. for six hours. The pressure must not be allowed to exceed 10 atmospheres. The resulting mass, which is quite free from objectionable odor of whale oil, may be worked up into soap, or the fatty acids present may be liberated and distilled. The yield of fatty acids so liberated is about 85 per cent. of the quantity taken originally. The hydrogen liberated during the reaction may be collected and utilized (*Chem. Eng. and Manufacturer,* 1916, 24, 203–204, by W. Schrauth, through *The Analyst,* March, 1917, p. 91).

URINARY TEST FOR TRINITROTOLUENE (T. N. T.).—The method mentioned was first described by Webster and is as follows: 12.5 c.c. of urine is mixed with an equal volume of 20 per cent. acid sulphuric, and then extracted in a separating funnel with ether. The ethereal extract, after washing with water, is tested for trinitrotoluene by adding 5 per cent. alcoholic solution of KOH; if a purple color makes its appearance, which quickly turns to brown, the presence of trinitrotoluene is positively indicated (*Medical Press,* 1916, 537, through *The Analyst,* March, 1917, p. 89).

THERAPEUTIC WORTHLESSNESS OF PIPERAZINE AND OTHER ORGANIC URATE "SOLVENTS."—Hanzlik in the *Jour. Laboratory and Clinical Medicine* makes some statements in reference to the unreliability of this class of drugs in doing what is claimed for them. Maybe not so much now, but twenty-five years ago piperazine was much vaunted as a wonderful agent for promoting diuresis, and acting as a urate solvent. The investigator mentions that while excessive doses show a slight increase in the uric acid output, the same result can just as readily be brought about by giving the patient such well-known alkali salts as sodium bicarbonate or the citrates,

and, what is more to the point, at a great saving in price. He found that the solvent action of piperazine on calculi is practically negligible in weak solutions, although in more concentrated solutions there seemed to be some solvent action; however, it was very limited. No evidence was obtainable that this drug can prevent or remove urate deposits. While it was found that the direct addition of piperazine to urine renders the liquid alkaline, this does not occur when the drug is taken internally, for the reason that it is destroyed in its passage through the body and is without effect on the urine. He also brings out the interesting fact that piperazine does not influence diuresis, and that its administration is without value in the treatment of gout. The author also makes the statement that there is sufficient scientific evidence to prove that many of the so-called urate solvents, such as the following, are absolutely without any value in that direction: Urosin, lycetol, sidonal, quinic acid, lysidin, urol, quinoline, our old friend colchicum, and piperazine. At this point we cannot help but remark that probably the best diuretic is, after all, water (through *J. A. M. A.*, 807, 1917).

PITUITARY EXTRACT IN OBSTETRIC PRACTICE.—The fact that this drug very often exhibits powerful physiological action is a sufficient reason for insisting that it be administered, if administered at all, with the greatest caution. In selected cases, it is an exceedingly active oxytocic, and is without equal in that regard, yet the drug should never be used in normal obstetrics. The writer of this paper makes this last assertion very plain and gives good reasons for it. It is said that a number of cases had rupture of the uterus, and other ill effects followed its incautious use (*Amer. Jour. Obstet.; Med. Review*, p. 444, 1917).

CURRENT LITERATURE

PHARMACOLOGICAL STUDIES WITH COCAINE AND NOVOCAINE.

George B. Roth (Bull. No. 109, Hygienic Laboratory) has made a comparative investigation of these substances in intact animals and on isolated organs.

The results of the laboratory experiments with cocaine and novocaine, when compared with the results obtained in the clinical use of these substances, show that man is relatively more susceptible to cocaine and novocaine than are laboratory animals. From animal experiments it is seen that the toxicity of these substances depends partly upon the manner and method of administration. The state-

ment also seems to hold true for man. The untoward results that have been reported in the literature from the use of novocaine in operations about the head and face might well be accounted for by the fact that absorption may be very rapid, as for example in dental operations when the injection is made in a region well supplied with blood vessels, so that administration directly into the circulation is not unlikely to occur, and when injected in this way the toxicity is greater than when given subcutaneously. Individual susceptibility is marked in both animals and man. This may account for some of the fatalities reported in the literature.

In addition to idiosyncrasy, age seems to be a factor in man in the production of fatal results with novocaine. In the three cases reported by Scandola, 1915, the ages of the men were 69, 75, and 80 years, respectively. In cases having low blood pressure, or cardiac disease, novocaine should be used with caution, inasmuch as in the laboratory experiments it has been shown to have a depressing effect upon the heart muscle when large doses are given.

The administration of hyoscine, previous to the use of a local anesthetic agent, is sometimes advised. If it is given before either cocaine or novocaine, it may act as a synergistic agent in depressing the respiration. In order to prevent the absorption of novocaine from the subcutaneous tissues, epinephrine is employed. Epinephrine is a relatively unstable agent, especially in alkaline solutions. It is not unlikely, therefore, that unless the epinephrine which is used with novocaine is active, general symptoms may arise from the administration of novocaine as a local anesthetic agent.

The melting point of novocaine, as determined from the examination of 10 samples used in this investigation, varied from 153° to 157° C. The relative toxicity of cocaine and novocaine, as shown by animal experiments, varies; the variation being dependent mainly upon the animal employed as test animal. The relative toxicity of cocaine and novocaine for various animals when given subcutaneously is as follows: For frogs (*Rana pipiens*) the ratio is 1.0 to 1.4; mice, 5.5 to 1; rats, 10 to 1; guinea pigs, 10 to 1; and rabbits, 5.3 to 1. When given intravenously to rabbits, the ratio of toxicity of cocaine to novocaine is 3.9 to 1. When given intravenously the rate of administration is a factor in modifying the toxicity. The subcutaneous administration of large sublethal doses of novocaine in the dog and cat causes marked general symptoms which rapidly subside. The ratio of the toxicity of cocaine and novocaine for mice, when fed on cakes containing these substances, is much wider than

when given in any other way, cocaine being about 50 times as toxic as novocaine. Feeding mice on sublethal doses of novocaine for a period of weeks did not seem to confer immunity to cocaine when the mice were fed on cocaine in the same way.

The effects of novocaine on the isolated heart of the frog resemble the effects produced by cocaine, both substances causing a decrease in rate of the heart and a decrease in the extent of systole. The relative toxicity on the heart of the frog as determined by perfusion experiments is less for novocaine than for cocaine. On smooth muscle, the effect of novocaine differs slightly from that produced by cocaine. On the isolated ureter of the dog, the isolated urinary bladder and stomach of the cat, and the isolated uterus of the rabbit, the effect of novocaine differs from that of cocaine only in being stimulating to a less degree when similar dilutions are used. On the isolated intestine of the rabbit, cocaine stimulates in dilute solutions, and in concentrated solutions depresses intestinal motility, whereas novocaine depresses it in any effective concentration. On the blood pressure and respiration, both cocaine and novocaine increase blood pressure and respiration in small doses and depress in large doses. When given subdurally, the relative toxicity of cocaine and novocaine is practically the same, as shown by the comparative effects on the blood pressure and respiration. Death in rabbits after cocaine or novocaine poisoning is usually respiratory, but with novocaine under certain conditions, death may be cardiac.

1. Novocaine is several times less toxic for laboratory animals than cocaine, the relative toxicity being dependent upon the method of administration as well as upon the animal used in making the determination.

2. Novocaine possesses many of the properties of cocaine as shown by experiments on the isolated heart, on smooth muscle, and by its effects on the circulation and respiration of anæsthetized animals.

3. The depressing effect of novocaine on the blood pressure and respiration of animals makes it necessary to use caution in its administration in clinical cases in which the blood pressure is low or in which the heart is at fault.

4. Great care should be exercised in the injection of novocaine subcutaneously, in order to avoid its entrance into the circulation, thereby increasing its toxicity.

5. Individual susceptibility should always be considered in the administration of either cocaine or novocaine.